# Opening and closing kinematics of fresh and calcified aortic valve prostheses: An in vitro study

Farhad Bakhtiary, MD,[a] Omer Dzemali, MD,[a] Ulrich Steinseiffer, PhD,[b] Christof Schmitz, PhD,[b] Birgit Glasmacher, PhD,[b] Anton Moritz, MD, PhD,[a] and Peter Kleine, MD, PhD[a]

**Objectives:** In vitro testing of biologic valves has been performed using only fresh but treated valves suitable for patient implantation. The present study investigates changes in hemodynamic performance and leaflet kinematics in progressively calcified porcine and pericardial aortic valve prostheses.

**Methods:** Edwards Perimount Magna (Edwards Lifesciences, Irvine, Calif) (n = 5) and Medtronic Mosaic Ultra (Medtronic Inc, Minneapolis, Minn) (n = 5) heart valves (23 mm) were investigated in an artificial circulation system (70 beats/min, cardiac output 5 L/min). Leaflet kinematics were visualized with a high-speed camera (3000 frames/sec). Valves were then exposed to a calcium-phosphate solution at a constant pulse rate of 300 beats/min for a total of 6 weeks. Repeated testing was performed after 1, 2, 3, 4, and 6 weeks of calcification. The calcification process might not be similar to in vivo performance.

**Results:** Initially, the Perimount Magna valves demonstrated lower pressure gradients compared with the Mosaic Ultra valves (9.7 ± 0.36 mm Hg vs 14.0 ± 1.16 mm Hg), but they showed higher closing volume and leakage flow. Total energy loss was equivalent after 1 week of calcification. Perimount Magna valves calcified significantly faster and more severely, leading to an increase in gradients and closure volume. Leaflet kinematics showed progressively longer opening and closing times for the pericardial valves (closing time Perimount Magna 135 ± 11 msec vs Mosaic Ultra 85 ± 9 msec after 6 weeks).

**Conclusions:** On the basis of visual inspection, despite the new ThermaFix (Edwards Lifesciences) tissue treatment, the Perimount Magna pericardial valves calcified in vitro faster and more severely than did the Mosaic Ultra porcine valves, which demonstrated a more constant performance throughout the calcification process. Leaflet kinematics showed a progressive prolongation of opening and closing times for pericardial valves, leading to higher closing volume.

From the Department of Thoracic and Cardiovascular Surgery of Johann Wolfgang Goethe University Hospital,[a] Frankfurt/Main, Germany; and Cardiovascular Engineering Group, Helmholtz Institute,[b] Aachen, Germany.

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Address for reprints: Farhad Bakhtiary, MD, Department of Thoracic and Cardiovascular Surgery, Johann Wolfgang Geothe University Hospital, Theodor-Stern-Kai 7, 60596 Frankfurt/Main, Germany (E-mail: farhad@bakhtiary.de).

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The primary function of aortic valves is prevention of backward flow from the aorta into the left ventricle (LV) during diastolic relaxation. However, investigations of aortic valve replacement, especially in vivo studies, focus mainly on forward flow and consider transvalvular gradients and effective orifice area (EOA) the most important determinants of prosthetic valve performance,[1-4] whereas the diastolic characteristics such as closing volume and leakage flow have not been investigated in such detail. The focus on systolic performance led to recent modifications of biologic aortic valves aimed at maximal valve opening without attention to the consequences for valve closure. This limited view on prosthetic aortic valve function is partly attributable to a lack of methods to study valve closure in vivo. Therefore, in vitro studies still play an important role in the investigation of biologic aortic valve prostheses.[5-7]

**Abbreviations and Acronyms**
EOA = effective orifice area
LV = left ventricle

In vitro studies have some inherent limitations, such as nonphysiologic contraction of the artificial LV, with the consequence of an abnormal flow pattern through the aortic valve. In addition, only fresh biologic valve prostheses were investigated for hemodynamic performance in vitro, whereas changes in leaflet motion caused by progressive degeneration will contribute to the increased mortality after aortic valve replacement compared with the background population.[8,9]

The aim of the present study was to achieve a more complete view of biologic valve function. We investigated the hemodynamic performance and durability of 2 biologic valves (1 porcine and 1 pericardial prosthesis), especially focusing on leaflet kinematics and its consequences for valve opening and closure. Fresh and progressively degenerated valves were tested in an in vitro setup. The 2 selected valves represented the most recent supraannular modifications of well-known aortic valve substitutes aiming in maximization of EOA.



## Materials and Methods

The study was performed in cooperation between the Department of Thoracic and Cardiovascular Surgery at the J. W. Goethe University Frankfurt am Main, Germany, and the Cardiovascular Engineering Group at the Helmholtz Institute Aachen, Germany.

Five porcine (Mosaic Ultra, Medtronic Inc, Minneapolis, Minn) and 5 pericardial (Carpentier Edwards Perimount Magna, Edwards Lifesciences, Irvine, Calif) aortic valve prostheses, 23 mm in size, were tested in a previously described artificial circulation system (Figure 1).[10]

### Medtronic Mosaic Ultra

This third-generation biologic valve is a sewing ring modification of the supra-annular Mosaic valve, which has been available for more than a decade. Its characteristics are Physiological Fixation (Medtronic Inc) with zero pressure on the leaflets during the fixation process with glutaraldehyde and anticalcification treatment with alpha-aminooleic acid.

### Perimount Magna

This latest modification of the extensively studied Perimount valve is characterized by glutaraldehyde fixation, the new ThermaFix (Edwards Lifesciences) anticalcification treatment, and a true supraannular design to maximize EOA.

### In Vitro Tests

At a constant hemodynamic level (cardiac output of 5 L/min, 70 beats/min), standard in vitro testing was performed (mean systolic pressure difference, EOA, closure volume, leakage flow), followed by calculation of systolic, diastolic, and total energy loss. Energy loss was defined as the time integral of the product of the mean systolic gradient and aortic flow during a defined interval such as systolic duration (systolic energy loss), closing interval (closing energy loss), or leakage duration (leakage energy loss). Energy loss values are expressed in the percentage of ventricular work load.

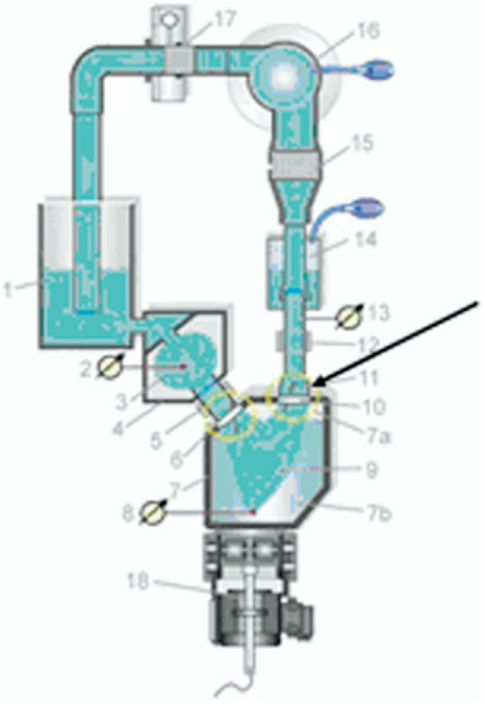


**Figure 1. Pulsatile artificial circulation system (position of the aortic valve, *arrow*): To create physiologic pressure and volume courses, flow resistors (15, 17) and programmable wind kettles (14, 16) are used. The flexible left silicone ventricle (9) and the rigid aortic root (11) simulate physiologic geometry. The volume expulsion of the simulated LV is created by electrohydraulic impulsion (18). Additional air within the compression housing (7a) serves as variable ventricular compliance. The computer-controlled volume extrusion allows an exact and reproducible simulation of the physiologic ventricular work.**

Leaflet kinematics were recorded using a high-speed camera (300 frames/sec). Three heart cycles were taped for further evaluation. The movies were evaluated for beginning and end of leaflet motion for valve opening (opening time) and beginning and end of leaflet motion for valve closure (closure time).

### Valve Calcification

After the initial test run, all prostheses were incorporated into a pulse duplicator running at 300 beats/min. The valves were irrigated with a calcium-phosphate solution to imitate calcific valve degeneration. This in vitro method of calcification using calcium-phosphate at a physiologic pH and temperature has been used and investigated previously, demonstrating results comparable to

**TABLE 1. Opening and closing times of Mosaic Ultra (Medtronic Inc, Minneapolis, Minn) and Perimount Magna (Edwards Lifesciences, Irvine, Calif) valves during progressive calcification**

| | Fresh | 1 | 2 | 3 | 4 | 6 |
|---|---|---|---|---|---|---|
| Magna | | | | | | |
| Opening time (msec) | 48 ± 10 | 53 ± 12 | 53 ± 10 | 54 ± 14 | 54 ± 12 | 55 ± 12 |
| Mosaic | | | | | | |
| Opening time (msec) | 27 ± 6 | 28 ± 10 | 26 ± 9 | 28 ± 10 | 28 ± 11 | 28 ± 8 |
| Magna | | | | | | |
| Closure time (msec) | 111 ± 12 | 121 ± 14 | 130 ± 15 | 128 ± 15 | 133 ± 14 | 135 ± 16 |
| Mosaic | | | | | | |
| Closure time (msec) | 74 ± 10 | 74 ± 9 | 74 ± 13 | 76 ± 11 | 77 ± 13 | 77 ± 9 |

All differences between Mosaic and Magna valves are statistically significant ($P < .001$).

in vivo valve degeneration.[11,12] The higher pulse rate accelerates the calcification process as additional mechanical stress is applied to the leaflets.

During the first 4 weeks, valves were taken out of the pulse duplicator weekly to undergo photography, hemodynamic testing, and leaflet kinematics recording with the high-speed camera. The valves were subjected to an additional 2 weeks of calcification and then tested as noted above. The valves were then investigated for calcium uptake within the leaflet tissue.

### Statistical Evaluation

For the statistical analysis of baseline characteristics and outcomes for the 2 valves, the Student *t* test and Fisher exact test were used. The results are reported as the mean ± standard deviation in text and Table 1.

## Results

The results are divided into 3 sections: hemodynamic results, progressive calcification results, and leaflet kinematics results.

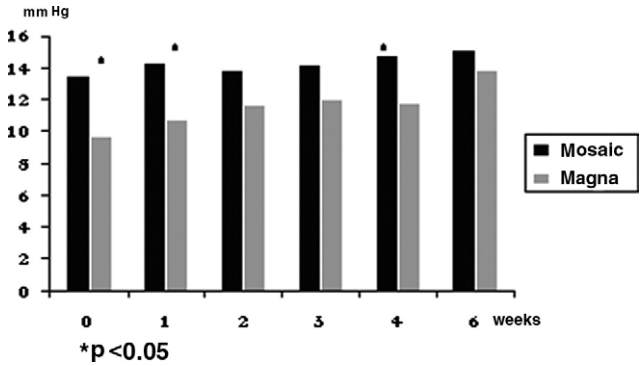


**Figure 2. Systolic pressure difference (transvalvular gradients) for the 2 fresh valves, which are treated valves suitable for patient implantation. Significantly lower values for fresh pericardial valves (0) were observed compared with the porcine prostheses. This difference narrowed during the test period of 6 weeks and was not statistically significant at the 2-, 3-, and 6-week measurements.**

### Hemodynamic Performance

Hemodynamic testing of the fresh and progressively degenerated valve prostheses revealed the following results.

***Transvalvular gradients.*** Systolic pressure difference demonstrated significantly lower values for fresh Magna valves (mean 9.7 ± 0.36 mm Hg) compared with the fresh Ultra prostheses (mean 14.0 ± 1.16 mm Hg) ($P < .05$). This difference narrowed during the test period of 6 weeks and was not statistically significant at the 2-, 3-, and 6-week measurements (Figure 2).

***Effective orifice area.*** EOA was significantly larger for fresh Magna valves (1.88 ± 0.06 $cm^2$ vs 1.46 ± 0.08 $cm^2$, $P < .01$); this difference also narrowed during the experimental period but remained statistically significant ($P < .05$ for the remaining measurements) (Figure 3).

***Closure volume.*** Closure volume was significantly lower for the fresh Mosaic valves (0.39 ± 0.08 mL vs 1.65 ± 0.11 mL, $P < .001$). This difference remained highly significant ($P < .001$) throughout the entire degeneration period. If leakage flow through the closed valve (closing volume) is also considered, this difference was even more pronounced (1.3 ± 0.11 mL for fresh Mosaic vs 5.1 ± 0.31 mL for Magna valves) (Figure 4).

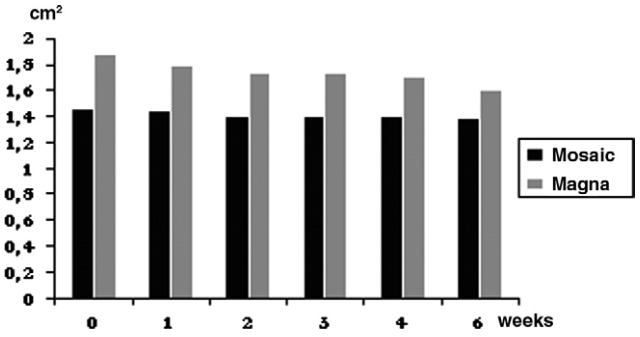


**Figure 3. EOA demonstrated significantly larger results for pericardial valves throughout the observation period ($P < .05$), with some narrowing with progressive degeneration. *EOA*, Effective orifice area.**

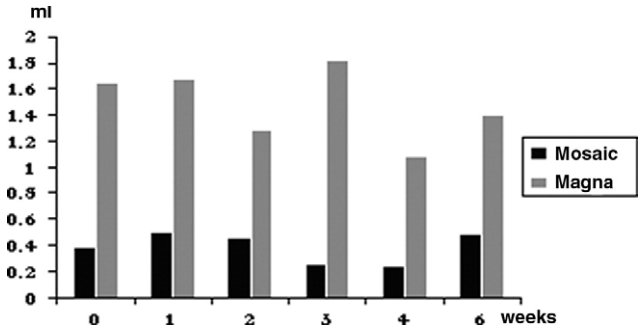


**Figure 4. Closure volume showed highly significant higher results for pericardial valves at each point ($P < .001$).**

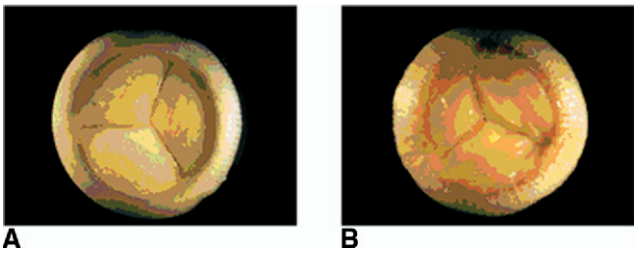


**Figure 6. A typical example of leaflet kinematics for both valves, pericardial (A) and porcine (B), after 3 weeks of degeneration.**

***Total energy loss.*** The combination of systolic, closure, and leakage energy demonstrated comparable results for the 2 valves (9.2% ± 1.21% vs 9.6% ± 1.11%); however, there was no difference after 1 week. The higher systolic energy loss of the Mosaic valves and the higher closure and leakage energy loss of the Magna valves equalized each other, leading to almost identical results for the total energy loss (Figure 5).

## Valve Calcification

Magna valves calcified faster and more diffusely compared with the Mosaic valves (Figure 6). Even after 1 week of calcification, 3 of 5 pericardial valves demonstrated visible deposits of calcium on the leaflet side that was oriented toward the LV (rough side of the pericardium). After the complete 6-week observation period, all Magna valves demonstrated significant diffuse calcification. Only 1 of 5 Mosaic valves demonstrated significant calcification of the leaflets; the remaining prostheses had only minor calcium deposits at the boundary between the leaflets and the stent. The amount of calcium uptake in the 2 bioprostheses was documented by the photographs but not objectively measured, because the study intended to mainly investigate the impact of valve calcification on the leaflet kinematics.

## Leaflet Kinematics

Opening and closure times of the 2 valve prostheses are listed in Table 1. Valve opening was seen at the exact same time point for the 2 valves, but beginning of valve closure was delayed for the pericardial valves. Mosaic porcine valves opened and closed significantly faster throughout the complete observation period of 6 weeks ($P < .01$). Whereas the leaflet kinematics remained stable for the Mosaic valves, there was a tendency toward longer opening times and a significant increase in closure times for the pericardial Magna valves. With progressive calcification, 1 of the Magna valves demonstrated an incomplete opening of 1 of the leaflets at the 6-week high-speed movie investigation. Almost all pericardial valves showed a small central opening at the coaptation zone of the 3 leaflets, explaining the increased leakage flow (Figure 7).

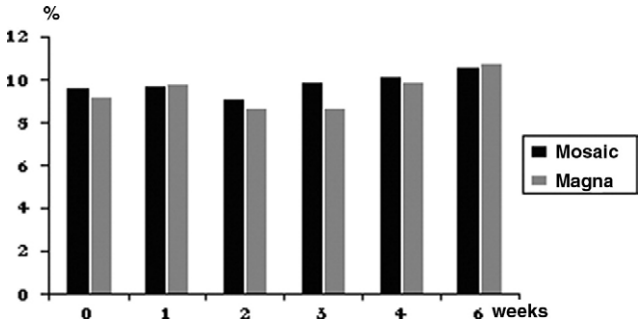


**Figure 5. Total energy loss (% of work load) was comparable for pericardial and porcine valves. A higher systolic energy loss for the porcine valves was equalized by lower diastolic energy losses.**

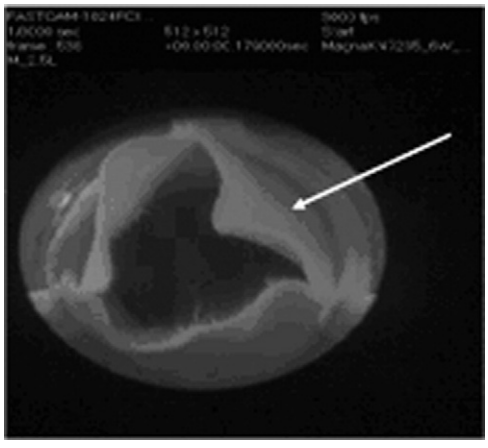

**Figure 7. Incomplete opening of one pericardial leaflet (*arrow*) after 6 weeks of progressive calcification. Mean pressure gradient in this valve was 18 mm Hg.**

## Discussion

Biologic aortic valve replacement has generated increasing interest over the past decade, partly because of the aging patient population and partly because of the reported excellent durability of second- and third-generation biological valve prostheses.[13-15] The 2 major determinants of long-term outcome are hemodynamic performance and durability of the implanted valves.

Most of the commercially available biologic valves consist either of porcine aortic leaflets or bovine pericardium. No randomized studies of patient outcome with large patient numbers comparing these 2 designs have been published, but a tendency toward lower transvalvular gradients for the pericardial valves has been reported.[13,14] However, some groups showed that long-term survival seemed to favor the porcine prostheses.[16,17] Factors other than pressure gradients and EOA may also contribute significantly to the clinical outcome after aortic valve replacement.

The present study aimed at gaining a detailed view of biologic valve performance with the special focus on valve closure and changes of leaflet kinematics with progressive calcification. The 2 selected valves were labeled 23 mm; however, studies comparing Perimount Magna with Medtronic Mosaic valves demonstrated smaller metric diameters for the Mosaic valve, leading to the ability to implant larger valve sizes in 28.4% for the porcine valve compared with only 8.3% for the pericardial valve.[18,19] However, the authors decided to compare identically labeled valve sizes to avoid misunderstanding.

Our study confirmed the excellent systolic performance of the fresh Magna valve, but this advantage disappeared to a certain extent so that the difference was no longer significant after 2 weeks of in vitro calcification. This observation was explained by the fast initiation of the calcification process for the pericardial valves despite the new ThermaFix anticalcification treatment. The observed increase of systolic pressure differences was also observed in vivo for standard Perimount valves by Banbury and colleagues.[16] EOA also favored the Magna prostheses. The large valve opening could be observed in the high-speed movies, with the pericardial leaflets moving completely out of the area of forward flow. However, this extensive leaflet motion during valve opening led to the delayed beginning of valve closure and significantly longer closure times. As a consequence, higher closure volumes were seen for the Magna prostheses, leading to an equivalent total energy loss. Valve incompetence was reported in vivo with transition from Grade 0 or Trace to Grade 1+, then to Grade 1+ or 2+, and finally to Grade 3+ or 4+ (14).

Mosaic valves showed higher transvalvular gradients and smaller EOAs, especially for fresh valves. The high-speed movies demonstrated a less-extensive leaflet motion compared with the Magna valves, so the systolic energy loss can be explained by the tissue and stent material within the forward flow area. On the other hand, this more physiologic valve opening led to fast and competent valve closure so closure volumes matched the results of native human aortic valves.[18] The absence of regurgitation was also reported clinically for standard Mosaic valves.[15] The porcine tissue treated with alpha-aminooleic acid resisted the in vitro classification method, so the hemodynamic results remained almost stable throughout the experiment. No valve malfunction could be observed.

On comparison of the 2 valve designs, one might summarize that the Magna pericardial valve was designed for maximal opening and thus matched the current opinion that systolic performance determines valve function and patient outcome.[20-22] The price paid for maximizing the leaflet movement away from the coaptation zone is delayed and slow valve closure. If we consider valve closure as the primary function of a valve, the Magna valve failed to mimic physiology. It is not surprising that the use of native porcine valve leaflets in the Mosaic Ultra model led to leaflet motion closer to physiology. The need for stent mounting of the leaflets resulted in some restriction of forward flow leading to higher gradients (maximal difference of 4 mm Hg), but the leaflet motion allowed earlier and faster closure.

The main goal in aortic valve replacement is good quality of life for our patients and a long-term survival comparable to that of the background population. This can be achieved by a valve that imitates a healthy native human valve and avoids lesions that impact ventricular function (stenosis and regurgitation). First, the primary function has to be matched: an early, fast, and competent closure. Here, the porcine Mosaic Ultra valve demonstrated lower regurgitant flows compared with the pericardial prosthesis. Second, the valve opening has to be considered with favorable results for the pericardial Magna prosthesis. The investigation of leaflet kinematics using a high-speed camera delivered the explanation for the systolic and diastolic hemodynamic results. In regard to the susceptibility to calcification, the pericardial tissue seemed to show a tendency toward faster and more severe calcification regarding photographic documentation.

## Limitations

In vitro calcification of the aortic valves eliminates the individual factor of valve degeneration, which requires large patient numbers for in vivo studies. Also, the method used in the present study has been verified. However, this is still an in vitro experiment with all of the limitations. Of course, the process of valve calcification might be different in the individual patient. The calcification was measured by visual inspection. The prostheses were of equivalent labeled sizes but necessarily equivalent sizes to fit a similar annulus.

The valves were removed from the calcifying solution for hemodynamic testing each week, so the calcification process might have been interrupted and thus affected the outcome. However, this was identical for all valves tested. A follow-up study with calcification for 4 weeks in a row is planned. Further investigation is needed to demonstrate the clinical relevance of our findings.

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